REMARKS

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claim Amendments

Claims 1, 16 and 17 have been amended to specify that the hyperlipidemic agent is a fibrate compound. Claim 3 has been amended to specify that the fibrate compound comprises fenofibrate or a salt thereof. Claims 12 and 20 have been amended to recite that the pharmaceutical composition is an agent for the treatment of diabetes.

Claims 4, 5, 14 and 22 have been cancelled, without prejudice.

No new matter has been added to the application by these amendments.

Consideration After Final Rejection

Although this amendment is presented after final rejection, the Examiner is respectfully requested to enter the amendments and consider the remarks, as they place the application in condition for allowance.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 12, 14, 20 and 22 as being indefinite under 35 U.S.C. § 112, second paragraph has been rendered moot by the above-discussed claim amendments.

Patentability Arguments

The patentability of the present invention over the disclosure of the reference relied upon by the Examiner in rejecting the claims will be apparent upon consideration of the following remarks.

Rejection Under 35 U.S.C. § 103(a)

The rejection of claims 1-3, 6-17 and 19-22 under 35 U.S.C. § 103(a) as being unpatentable over Bussolari et al. (US 2003/0045553) is respectfully traversed.

The Position of the Examiner

The Examiner takes the position that Bussolari et al. disclose a composition for administering one or more glucose readsorption inhibitor and one or more PPAR modulator for the treatment of diabetes or Syndrome X, also known as metabolic syndrome. The Examiner states that Bussolari et al. disclose the specific PPAR modulator fenofibrate, and the specific α-glucosidase inhibitor voglibose.

The Examiner admits that Bussolari et al. do not specifically disclose the combination of fenofibrate and voglibose. However, the Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time of the invention to practice the invention of Bussolari et al. as the specific combination of fenofibrate and voglibose.

Additionally, in response to Applicants' previous arguments, the Examiner asserts that, as evidenced by Van Gaal et al., agents for controlling postprandial glucose, agents for controlling fasting plasma glucose, and their use in combination therapy are known in the prior art for the same purpose of treating Type 2 diabetes. The Examiner also takes the position that the data set forth in Applicants' Examples is not clear and convincing.

Applicants' Arguments

Applicants respectfully disagree with the Examiner's position for the following reasons.

Please see pages 12-14 of Applicants' response filed April 21, 2008 for a discussion of the Bussolari et al. reference.

Van Gaal et al. (Diabetologia (2003) 46: M44-M50) disclose that the introduction of multiple classes of oral antidiabetic agents that act differentially to correct the metabolic defects which characterize Type 2 diabetes has greatly expanded the potential for combination therapy (page M45, left column, first paragraph). Additionally, Table 1 on page M45 shows classification and mode of action of oral antidiabetic agents with potential for use in combination therapy. Table 1 also shows that the mode of action of α-glucosidase inhibitors such as acarbose is to "reduce intestinal breakdown of complex carbohydrates," and the primary control thereof is postprandial glucose.

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(A) Difference between α-glucosidase inhibitor and glucose reabsorption inhibitor

The α-glucosidase inhibitor, such as voglibose, does not belong to the category of the glucose reabsorption inhibitor, as evidenced by the following detailed arguments (i), (ii) and (iii).

(i) Difference between absorption and reabsorption of glucose

Ingested carbohydrates are firstly decomposed in an alimentary canal into monosaccharides, such as glucose, and the monosaccharides are absorbed with an intestinal canal.

On the other hand, the glucose reabsorption inhibitor is originally an agent for deteriorating blood sugar by inhibiting reabsorption of glucose in a kidney, as shown by its name.

As apparent from the fact that reabsorption of glucose occurs in the kidneys, not the intestinal tract, it is easily understandable that absorption of glucose in the intestinal canal is clearly different from reabsorption of glucose in the kidneys, from both a medical and a scientific view point.

Diet therapy is a long-established therapy for diabetes and is a technique for deteriorating absorption of nutrition, such as glucose, with an intestinal canal. As a result of deteriorating absorption of nutrition with the intestinal canal, the digestion and absorption of nutrition to a body also deteriorate. Thus, a person skilled in the art clearly knows or understands that such a diet therapy technique is not related to reabsorption of glucose in kidneys, as disclosed by Bussolari et al.

(ii) α-glucosidase inhibitor (α-GI)

The action of the α-GI is to inhibit the metabolism to delay the absorption of glucose. The action of the α-GI is neither deteriorating digestion and absorption of glucose nor reabsorption of glucose in kidneys. These facts are evidenced by the following description of Cecil Textbook of Medicine, W.B. Saunders, ed. By L Goldman and J.C. Benett, 21th edition, page 127, "Acarbose and miglitolare, reversible inhibitors of α-glucosidase (the intestinal enzymes that break down complex carbohydrates into monosaccharides), delay the absorption of carbohydrates such as starch, sucrose, and maltose. It does not affect absorption of

monosaccharides such as glucose." (Emphasis added.) (A copy of this reference page is attached hereto.)

That is, the delay of the absorption of nutrition, such as glucose, would not influence or relate to deterioration in absorption of glucose. This is because, an intake of the α-GI causes decomposition of nutrition, such as carbohydrates, by a coliform bacteria in the colon, even if the metabolism is delayed. As a result, an increase in blood sugar is observed later than usual. Thus, a person skilled in the art would naturally understand that the total amount of glucose absorbed into blood does not change.

Therefore, a pattern of the concentration of the blood glucose obtained by administration of the α-GI is not the same as a pattern of the blood glucose concentration obtained by use of the glucose reabsorption inhibitor. In other words, the pattern of the blood glucose concentration similar to that obtained by use of the α-GI would never be obtainable, even if the glucose reabsorption inhibitor is administered.

On the other hand, Applicants do aim to the α-GI, which delays digestion and absorption of nutrition, but does not decrease them. Regarding the α-GI, Applicants considered that the action of the α-GI is to delay digestion and absorption of the nutrition. Applicants also considered side effects accompanied by a sudden or drastic deterioration of blood glucose due to administration of a glucose absorption inhibitor, a glucose reabsorption inhibitor, insulin, an insulin secretion accelerator or the like, and considered that postprandial hyperglycemia leads to causes of various diseases, at the time when the invention was made. Thus, Applicants came to realize the possibility of combining the α-GI with a fibrate, such as fenofibrate. Applicants' invention was made based on the above considerations, as well as results of animal experiments.

(iii) Relationship between Bussolari et al. and the previously submitted document D

According to the previously submitted document D (Clinical Diseases of Adult People, Vol. 22, No. 3, 1992, pages 127-134), although the absorption inhibition of sucrose is very low by the α-GI administration, the maximum blood-sugar level remarkably deteriorates. Concretely, the absorption inhibition of 100 g of orally administered sucrose is 5.0±3.3 g (an average ± a standard deviation, N=12), i.e., only about 5%, by AO-128 administration. However, the maximum blood-sugar level is deteriorated from 136.8±16.6 mg/dl to 110.2±18.7 mg/dl as an

average, i.e., almost 20%.

More importantly, results for subjects No.1 and No.11 show great decrease in the maximum blood-sugar level, in spite of no inhibition in sucrose absorption. Concretely, although the values of absorption inhibition of sucrose are 0.1 g and 0 g for No.1 and No.11 respectively, the decrease in the maximum blood-sugar levels are 26 mg/dl (118 mg/dl → 92 mg/dl, 22% decrease) for No.1 and 33 mg/dl (130 mg/dl → 97 mg/dl, 25% decrease) for No.11. These data clearly lead to a result that the blood-glucose decreasing action of AO-128 does not depend on the inhibition of absorption of sucrose (or glucose).

According to document D, a clinical dosage of the α-GI AO-128 ensures suppression of a remarkable increase in a postprandial blood-sugar level, not because of a glucose absorption inhibition, but because of an effective use of glucose at any time in the lever or skeletal muscles. Further, the effective use of glucose is due to a delay in absorption of glucose. That is, the document D suggests that the main action of the α-GI in a clinical dosage is delay in absorption of glucose.

On the other hand, according to Bussolari et al., the Examiner presumes that the α-GI shows an anti-diabetes activity whereby inhibiting glucose absorption. However, such a presumption is clearly different from the above results or suggestions by document D.

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(B) Effects of the invention

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(i) Comparison proposed by the Examiner

Regarding the Groups 4, 5 and 7 of the Examples of the present specification, the Examiner compares ranges of GLU conc. between before and after loading as follows:

Table A

	GLU conc.(g/L)		GLU conc. change (g/L)	Overlap (g/L)
	before loading	after loading		
group 4 (Voglibose)	3.83-4.77 (4.30±0.47)	4.08-4.92 (4.50±0.42)	-0.69 (4.08-4.77)	4.08-4.77
group 5 (Fenofibrate)	3.71-4.81 (4.26±0.55)	4.44-5.12 (4.78±0.34)	-0.37 (4.44-4.81)	4.44-4.81
group 7 (Voglibose +Fenofibrate)	4.58-5.08 (4.83±0.25)	3.91-4.65 (4.28±0.37)	-1.17 (3.91-5.08)	4.58-4.65

(ii) Unreliability of the comparison proposed by the Examiner

Applicants respectfully assert that the Examiner's proposed comparison is untenable. A person skilled in the art knows it is inappropriate to evaluate pharmaceutical effects by the change between the maximum before loading and the minimum after loading, and/or overlap between before and after loading, because the compared values do not have the same standard.

For example, the values "4.30" and "4.50" for the group 4 are both mean values based on the results for the plurality of subjects. Thus, the above values are meaningfully comparable to each other as a difference between before and after loading from a view point of statistically reliable comparison. Such a fact is also well-known in the art.

On the other hand, the standard deviations such as "±0.47" and "±0.42" for the group 4 only show scatterings among the actual data of the subjects and have no substantial meanings. Thus, it is statistically meaningless to compare (a) an upper limit obtained by adding a standard deviation to an average with (b) a lower limit obtained by subtracting a standard deviation from an average.

If a comparison of the upper and lower limits according to the Examiner's suggestion is meaningful, the lower limit before loading and the upper limit after loading should be comparable as follows:

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Table B

	GLU conc.(g/L)		GLU conc. change (g/L)
	before loading	after loading	
group 4 (Voglibose)	3.83 (4.30-0.47)	4.92 (4.50+0.42)	1.09
group 5 (Fenofibrate)	3.71 (4.26-0.55)	5.12 (4.78+0.34)	1.41
group 7 (Voglibose +Fenofibrate)	4.58 (4.83-0.25)	4.65 (4.28+0.37)	0.07

The obtained changes are largely different from those calculated by the Examiner (and shown in the above Table A). As apparent from such a fact, it cannot be said that the comparison of upper and lower limits proposed by the Examiner is reliable.

(iii) Reliability of the results of the Examples

In order to clarify the reliability of the evaluation of the Examples, our client provides test results for each subject as follows:

Table C

I. Plasma concentration (g/L) of glucose in streptozotocin-treated rats
before and after sucrose loading

Groups	ID.No.	GLU concentration before loading(g/L)	GLU concentration after loading(g/L)	GLU concentration before loading(g/L)
group 4 STZ処置 Vog + CMC	11	5.27	4.47	-0.80
	15	5.41	5.83	0.42
	18	1.34	1.59	0.25
	35	*	*	*
	36	5.09	4.76	-0.33
	50	4.93	4.81	-0.12
	61	3.73	5.19	1.46
	67	5.31	4.77	-0.54
	76	4.79	5.55	0.76
	81	2.85	3.53	0.68
	Mean	**4.30**	**4.50**	**0.20**
	S.E.	**0.47**	**0.42**	
group 5 STZ処置 Feno + CMC	7	5.88	5.93	0.05
	14	1.65	3.66	2.01
	19	5.59	5.14	-0.45
	20	5.54	5.60	0.06
	23	1.75	2.76	1.01
	31	*	*	*
	43	4.77	4.48	-0.29
	44	4.68	5.33	0.65
	54	5.30	5.54	0.24
	69	3.14	4.60	1.46
	Mean	**4.26**	**4.78**	**0.53**
	S.E.	**0.55**	**0.34**	
group 7 STZ処置 Vog + Feno	10	*	*	*
	25	*	*	*
	47	5.70	4.97	-0.73
	55	5.19	4.94	-0.25
	63	4.52	4.01	-0.51
	65	5.38	4.56	-0.82
	66	4.96	4.73	-0.23
	68	3.40	1.77	-1.63
	80	4.41	4.65	0.24
	82	5.10	4.60	-0.50
	Mean	**4.83**	**4.28**	**-0.55**
	S.E.	**0.25**	**0.37**	

STZ; streptozotocin 45 mg/kg, i.v.
D.W.; distilled water
CMC; 1.5 % carboxymethylcellurose
Met; metformin 50 mg/kg, p.o.
Vog; voglibose 0.2 mg/kg, p.o.
Feno; fenofibrate 50 mg/kg, p.o.
*: No data because of subject's death
S.E.: standard error

Incidentally, the "rate of change (%)" in Table 1 of the present specification shows a rate of change between averages before and after loading.

As apparent from the above Table C, the data shown in the present specification is based on the actual test results for a plurality of animal subjects.

A change in GLU concentration between before and after loading sucrose is also shown in the above Table C for each subject. Moreover, an average (mean) of the changes of the subjects of each group is also calculated based on the change for each subject and shown in the Table C.

The average of changes in the subjects of group 4 (voglibose) is 0.20, that of group 5 (fenofibrate) is 0.53 and that of group 7 (voglibose + fenofibrate) is -0.55. That is, glucose concentration is enhanced after loading sucrose relative to before loading it in group 4 (only administration of voglibose) and group 5 (only administration of fenofibrate). On the contrary, glucose concentration is reduced after loading sucrose relative to before loading it in group 7 (co-administration of voglibose + fenofibrate). These results are also statistical, clearly. Further, even considering the fact that the average of changes in the subjects of group 4 (voglibose) is 0.2, that of group 5 (fenofibrate) is 0.53 the voglibose, it would never be predicted from the above results of groups 4 and 5 that the average of changes in the subjects of group 7 (voglibose + fenofibrate) provides a negative value, in particular, very small value like "-0.55".

As explained above, it can be said that the evaluation and results provided in the Examples of the present specification are quite proper.

Incidentally, since the above results are obtained by using animal subjects, there are scatterings among the evaluated GLU concentrations, naturally. A person skilled in the art knows that the results obtained by using animal subjects are usually scattered widely. Moreover, comparison of the averages is sufficiently reliable, even if there is an overlap between before and after loading mentioned by the Examiner. Such an overlap has no influence on the results

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obtained by the comparison of the averages.

For these reasons, the invention of Applicants' claims is clearly patentable over Bussolari et al. Accordingly, the above-rejection is untenable and should be withdrawn.
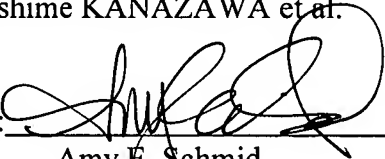
Conclusion

Therefore, in view of the foregoing amendments and remarks, it is submitted that each of the grounds of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

If, after reviewing this Amendment, the Examiner feels there are any issues remaining which must be resolved before the application can be passed to issue, the Examiner is respectfully requested to contact the undersigned by telephone in order to resolve such issues.

Respectfully submitted,

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Pharmacologic Intervention

ORAL GLUCOSE-LOWERING AGENTS. Several new classes of oral glucose-lowering agents have recently become available for the treatment of type 2 diabetes (Table 242–6, Fig. 242–7). These drugs are generally effective in patients in whom diet and exercise fail to achieve treatment goals. Oral agents tend to be favored as first-line therapy if hyperglycemia is mild, the patient is older, and obesity is more pronounced. The response cannot be predicted with certainty from clinical characteristics, and few circumstances contraindicate their use (e.g., severe insulin deficiency, allergy, pregnancy). Patients with severe hyperglycemia generally require insulin to lower glucose levels in the initial phases of treatment. Once glucose levels have stabilized and the "toxic" effects of severe hyperglycemia on beta cell function and insulin action have been minimized, many such patients become responsive to oral agents.

SULFONYLUREA. Sulfonylurea drugs were the only class of oral agents available in the United States before 1995. They act by enhancing insulin secretion by virtue of their ability to bind to their receptors associated with ATP-dependent potassium channels on the surface of the beta cell, thereby facilitating cellular depolarization. The reduction in glucose that follows is accompanied by a decline in insulin levels toward baseline. Insulin resistance commonly diminishes as a result of reversal of glucotoxicity. Because of their mechanism of action, sulfonylureas are totally ineffective in type 1 diabetes. Although the sulfonylureas differ in relative potency, effective dosage, duration of action, metabolism, and side effects, from a clinical standpoint these differences have marginal practical significance (see Table 242–6). Each drug has similar hypoglycemic effects when used in maximal doses. Drugs with a shorter duration of action that are metabolized by the liver have advantages in elderly patients with impaired renal function because such patients are more vulnerable to hypoglycemia, but they may be less effective because of problems with compliance with multiple dosing schedules. Longer-acting sulfonylureas require only once-per-day dosing but enhance the risk of hypoglycemia in patients who omit meals. Sulfonylureas with an intermediate duration of action may offer a reasonable compromise, although they still have a risk of producing severe hypoglycemia. These drugs may be given once per day, although twice-daily dosing may be required in patients with more severe hyperglycemia. After choosing an oral agent, treatment is initiated at low doses, with the dosage increased every 1 to 2 weeks until treatment goals or maximally effective doses are reached. Most patients initially respond with a lowering of glucose levels; however, about 15 to 20% of diabetic patients do not benefit (so-called primary failure). It is not uncommon to see loss of drug effect after years of therapy because of failure to sustain enthusiasm for diet and exercise, progression of beta cell failure, superimposition of other medical problems or drugs, or drug tolerance. The deteriorating glycemic control begets even poorer control as a result of glucotoxicity (see Fig. 242–4). Secondary drug failure occurs at a rate of 5 to 10% per year. Early signs of secondary drug failure should provoke renewed attempts to enforce diet, as well as a prompt increase in drug dosage. The appearance of hyperglycemia despite maximal drug doses signals the need to add another class of oral glucose-lowering agent (e.g., biguanide, or glucosidase inhibitor, thiazolidinedione) or to institute insulin therapy.

BENZOIC ACID DERIVATIVES. Repaglinide, a non-sulfonylurea which interacts with a different portion of the sulfonylurea receptor to stimulate insulin secretion, has recently been approved by the Food and Drug Administration (FDA). Its major advantage is its rapid and relatively short duration of action, which could potentially reduce the risk of hypoglycemia. The drug requires frequent daily dosing and must be taken at the beginning of each meal.

BIGUANIDES. Metformin (the only biguanide approved for use in the United States), unlike sulfonylureas, acts mainly by reducing hepatic glucose production. The cellular mechanism for this effect is, however, uncertain. Because its effect is extrapancreatic, insulin levels fall, a potential advantage if the theory implicating hyperinsulinemia in the development of atherosclerosis proves correct. Because metformin (unlike other oral glucose-lowering agents) may induce mild weight loss, it is particularly suitable for obese patients either as monotherapy or as an additive drug when other oral glucose-lowering agents are ineffective alone. The drug does not produce hypoglycemia when used as monotherapy; however, it can rarely produce lactic acidosis (approximately 0.03 cases per 1000 patient-years) and should therefore not be given to patients with renal insufficiency, liver disease, a history of congestive heart failure or chronic hypoxia, or alcohol abuse. The major side effects are gastrointestinal, particularly anorexia and nausea, which may contribute to its effect on weight loss. Metformin has a relatively short half-life (it is eliminated exclusively by the kidney), which generally necessitates administration as two or three divided doses given with meals.

THIAZOLIDINEDIONES. Thiazolidinediones reduce insulin resistance, most likely through activation of the peroxisome proliferator–activated receptor γ—a nuclear receptor that regulates the transcription of several insulin-responsive genes. Their biologic effect is mediated via stimulation of peripheral glucose metabolism. They have little effect on hepatic glucose production. Clinical studies demonstrate a reduction in both plasma glucose and insulin levels. Troglitazone was the first thiazolidinedione derivative approved for use in the United States. It is most effective when used in conjunction with insulin in type 2 diabetic patients who are not adequately controlled with insulin or in combination therapy with other oral hypoglycemic agents such as sulfonylureas. Troglitazone commonly requires 4 to 6 weeks for its glucose-lowering effect to be fully manifested. It has been reported to cause an increase in transaminases in about 2% of patients. Reports of cases of severe liver failure have led the FDA to recommend measuring liver enzymes at baseline every month for the first year of treatment and on a regular basis thereafter.

Recently, the FDA approved two new thiozolidinediones, rosiglitazone and pioglitazone, which are effective glucose-lowering agents either as monotherapy or in combination with other drugs. Preliminary data suggest that both drugs have a much lower risk of hepatotoxicity and therefore are more appropriate for use as monotherapy. Nevertheless, none of the thiozolidinediones should be used in patients with liver function abnormalities, and they should be discontinued if liver enzymes (e.g., ALT) become elevated. Hypoglycemia is rare when thiozolidinediones are used as monotherapy, but may occur when these drugs are used in conjunction with insulin or sulfonylureas. Weight gain and/or edema may also complicate thiozolidinedione therapy.

α-GLUCOSIDASE INHIBITORS. Acarbose and miglitolare, reversible inhibitors of α-glucosidases (the intestinal enzymes that break down complex carbohydrates into monosaccharides), delay the absorption of carbohydrates such as starch, sucrose, and maltose. It does not affect the absorption of monosaccharides such as glucose. To be effective, this class of drugs must be taken at the beginning of each carbohydrate-containing meal. In controlled trials performed in patients with type 2 diabetes, α-glucosidase inhibitors alone or as an adjunctive therapy to reduce postprandial hyperglycemia resulted in a small, but clinically meaningful reduction in glycosylated hemoglobin levels.

A major advantage is that α-glucosidase inhibitors do not have significant toxicity. The most common side effects are abdominal bloating, flatulence, and sometimes diarrhea. The adverse gastrointestinal effects are minimized by using a slowly escalating dose titration schedule in which treatment is initiated at the lowest dose.

INSULIN THERAPY. Insulin is most commonly used as 1st-line therapy for non-obese, younger, or severely hyperglycemic type 2 diabetic patients and is temporarily required during severe stress (e.g., injury, infection, surgery) or in pregnancy. Insulin should not be used as 1st-line therapy in poorly compliant patients who are unwilling to self-monitor glucose levels or for patients with a high risk of hypoglycemia. In patients with severe obesity, profound insulin resistance often necessitates the use of large doses of insulin, which sometimes interferes with efforts to restrict caloric intake to achieve weight loss. In patients with newly diagnosed diabetes or those with relatively mild fasting hyperglycemia who continue to maintain endogenous insulin secretory capacity, relatively small doses of insulin (e.g., 0.3 to 0.4 U/kg of body weight per day) given once or twice per day may be sufficient to achieve target goals. Such patients retain some degree of meal-stimulated endogenous insulin secretion and may therefore require less rapid-acting insulin. Although it is common practice to administer a single dose of intermediate-acting insulin in the morning, frequently its glucose-lowering effect does not extend over a full 24-hour period. Because a key element of successful insulin treatment is to dimin-